

## Editorial

# Markers of inflammation in unstable angina

Atherosclerosis can be seen as a dynamic chronic inflammatory process, in which flares of inflammatory and thrombotic activity underlie the clinical presentations of unstable angina and myocardial infarction.<sup>1,2</sup> In this issue of *Heart*, two articles draw attention to the inflammatory basis of acute coronary syndromes (ACS).

### More evidence for circulating activated leucocytes

The first study, by Hillis and colleagues,<sup>3</sup> focuses on expression and function of the  $\beta_2$  integrin CD11b/CD18 (Mac-1, CR3). The  $\beta_2$  integrins are a family of four heterodimers, in which separate  $\alpha$  chains (CD11a–d) combine with a common  $\beta$  chain (CD18). CD11b/CD18 (Mac-1, CR3) is critical for leucocyte adhesion and migration, and also acts as a receptor for complement C3bi. In addition, CD11b/CD18 is a signalling molecule and is necessary for many other neutrophil and monocyte effector functions in inflammation.<sup>4</sup> Both neutrophils and monocytes normally carry CD11b/CD18 on the cell surface, and also contain additional stores of the heterodimer in the membranes of intracellular granules. Translocation of granules to the cell surface upon cell activation therefore results in increased adhesion potential. Importantly, however, the adhesion function of CD11b/CD18 depends more on affinity and avidity changes than on the absolute level of expression, and these are thought to involve signalling events within the surface membrane and cytoskeleton and the binding of divalent cations. Despite this qualification, increased surface expression of CD11b/CD18 is commonly associated with increased adhesive function, and hence measuring CD11b/CD18 expression in clinical samples may provide useful indirect information.

Hillis and colleagues found increased expression of CD11b/CD18 on circulating neutrophils and monocytes of patients with unstable angina, and although the numbers were small, this appeared to occur in some patients in the absence of detectable increases in cardiac troponin I. Thus, inflammation may precede myocardial injury. Paradoxically, neutrophils from patients with unstable angina adhered less well than control neutrophils in an *in vitro* adhesion assay, reflecting the dissociation between integrin expression and function. As the authors point out, changes in integrin function can be rapid and transient, and we cannot assume that reduced adhesiveness *ex vivo* signifies reduced potential for leucocyte–endothelial cell and leucocyte–leucocyte interactions in the tissues.

The contribution from Hillis and colleagues<sup>3</sup> is consistent with previous studies which have indicated that neutrophil and monocyte activation occur in unstable angina, and that this may happen in the coronary circulation.<sup>5,6</sup> What exactly stimulates leucocyte activation in ACS is not known, but the result is likely to be an increase in leucocyte adhesion, not just to the unstable plaque, but also to downstream coronary microvascular endothelium. This in turn may lead to more widespread endothelial dysfunction through the release of oxygen free radicals and

proteases. Furthermore, CD11b/CD18 may promote leucocyte aggregation, which can further reduce myocardial perfusion through capillary plugging.

### Soluble VCAM-1 predicts outcome

The second article, by Mulvihill and colleagues,<sup>7</sup> highlights the use of soluble adhesion molecules as markers of inflammatory activity in ACS. E- and P-selectin, ICAM-1, and VCAM-1 are all adhesion molecules that show increased expression by endothelial cells in response to cytokines and other stimuli, and which are involved in guiding circulating leucocytes into inflamed tissues.<sup>8,9</sup> Initial tethering and rolling of neutrophils on vascular endothelium is mediated by transient interactions between selectins (L-selectin on leucocytes, E-selectin on activated endothelial cells, and P-selectin on both activated endothelial cells and activated platelets) and their glycosylated receptors on the opposing cell. While rolling, neutrophils become activated by local chemoattractants, resulting in the stimulation of firm adhesion through  $\beta_2$  integrin (CD11a/CD18, CD11b/CD18) interactions with ICAM-1 and ICAM-2. Monocytes may also employ these molecules and, additionally, may tether, roll, and firmly adhere through interactions between the  $\alpha_4$  integrin VLA-4 (CD49d/CD29) and VCAM-1. Since P-selectin, E-selectin, ICAM-1, and VCAM-1 are each shed from cell surfaces into extracellular fluid, concentrations of the circulating extracellular domains of soluble molecules have been considered to be a reflection of their surface expression in the tissues, and hence have been used as markers of inflammatory activity.<sup>10,11</sup> It is debatable whether circulating adhesion molecules are functionally important, or are merely awaiting clearance and degradation.

The study of Mulvihill and colleagues<sup>7</sup> sets out to determine whether measurement of concentrations of the four soluble adhesion molecules during acute presentation with unstable angina or non-Q wave myocardial infarction predicted outcome over six months of follow up, and to compare prognostic accuracy with C-reactive protein (CRP).<sup>12</sup> In a previous study, this group found that concentrations of all four soluble adhesion molecules were increased in patients with unstable angina or non-Q wave myocardial infarction. Now, they show that concentrations of soluble VCAM-1 correlated strongly with the occurrence of a major adverse cardiovascular event within six months, whereas concentrations of soluble P-selectin, E-selectin, and ICAM-1 do not. Although it would be a mistake to overinterpret these observations in terms of pathophysiology, it is interesting that ICAM-1 but not VCAM-1 has been found in prospective epidemiological studies to be a risk factor for future coronary events.<sup>11,13</sup> It is possible therefore that increased soluble VCAM-1 and ICAM-1 expression reflect the different facets of acute and chronic coronary artery disease. It is also possible that increased soluble VCAM-1 might reflect cardiomyocyte injury, since no information on troponin concentrations in these patients is provided.

If the degree of inflammation predicts outcome, what inflammatory markers might the clinician measure in patients upon presentation with unstable angina? Mulvihill

and colleagues found that a CRP concentration of  $< 3$  mg/l had a negative predictive value for major adverse cardiovascular events within six months of 97%.<sup>7</sup> Conversely a CRP concentration of  $> 3$  mg/l had a sensitivity of 96% for predicting adverse cardiovascular events, albeit with a specificity of 52%. CRP was as sensitive as soluble VCAM-1 for predicting major adverse events, and measuring VCAM-1 did not appear to add to CRP's predictive accuracy. Whether measuring cytokines such as IL-6 or surface expression of leucocyte activation antigens (for example, CD11b/CD18) provides further information remains to be determined, but arguably measurement of CRP, which is readily available and relatively cheap, may be sufficient for evaluating ongoing inflammation as a risk for poor outcome, particularly if measured at discharge rather than admission.<sup>14</sup>

### Therapeutic implications

What potential does the recent burst of information on inflammation and coronary artery disease have for influencing treatment? Although efficacy in animal models prompted the trial of anti- $\beta_2$  integrin antibodies in acute coronary syndromes, results from clinical trials have so far been disappointing.<sup>15</sup> While we continue to consider other options, we should not forget that drugs used currently may act partly through anti-inflammatory mechanisms. Although aspirin obviously has anti-inflammatory properties, at the low doses used in cardiological practice the main action is probably on platelets. On the other hand, inhibitors of the renin-angiotensin system may block the activation by angiotensin II of NADP(H) oxidase and subsequent superoxide production,<sup>16</sup> and also inhibit the activation by angiotensin II of endothelial cell NF $\kappa$ B activation and VCAM-1 expression.<sup>17</sup> Lastly, there is an emerging literature that HMG-CoA reductase inhibitors have anti-inflammatory and immunomodulatory actions that are not simply due to lowering cholesterol,<sup>18</sup> and it is possible that such properties might beneficially influence adverse events if a statin is introduced acutely in unstable angina.

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Presented to you by the BMJ Publishing Group (London, UK) and Institute for Healthcare Improvement (Boston, USA), with the support of the the Commonwealth Department of Health and Aged Care (Australia), Safety and Quality Council (Australia), NSW Health (Australia), and Ministry of Health (New Zealand).

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